A

OFGS File: P/1890-200(DIV)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Gary D. HODGEN Date: May 18, 1999

Serial No.: Unknown

Filed: Herewith

For: CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

Asst. Commissioner of Patents and Trademarks
Washington, DC 20231

REQUEST FOR CONTINUING APPLICATION UNDER 37 C.F.R. 1.53(b)

Sir:

This is a request for the filing of a Divisional application under the provisions of 37 C.F.R. 1.53(b) of pending application Serial No. 09/059,476, filed April 13, 1998, by Gary D. HODGEN, entitled CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS. The prior application is hereby incorporated by reference.

Enclosed is a copy of the prior application, including the oath or declaration as originally filed.

I hereby state that the attached papers are a copy of prior application Serial No. 09/059,476, filed April 13, 1998, without any new matter therein.

The filing fee is calculated as follows:

BASIC Filing Fee: .....$ 760.00
Number of Claims in Excess of 20: 0 x $18 .....
Number of Independent Claims over 3: 0 x $78 ....
One or more multiple dependent claims: $260.....$_____
TOTAL FILING FEE REDUCED 50% FOR SMALL ENTITY .....$ 380.00

SEND CORRESPONDENCE TO: DIRECT TELEPHONE CALLS TO:

OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403 (212) 382-0700
Customer No. 2352

EXPRESS MAIL CERTIFICATE

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee (mail label #EL010282840US) in an envelope addressed to: Asst. Commissioner of Patents and Trademarks, Washington, D.C. 20231, on May 18, 1999:

Dorothy Jenkins

Name of Person Mailing Correspondence

Dorothy Jenkins

Signature

May 18, 1999

Date of Signature

Respectfully submitted,

Edward A. Meilman

Edward A. Meilman
Registration No.: 24,735
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700

EAM:mgs

Serial or Patent No.: _____ OFGS File No. P/1890-162
Filing or Issue Date: _____
Applicant or Patentee: Gary D. Hodgen
For: CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
37 CFR 1.9(f) and 1.27(d) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF CONCERN: MEDICAL COLLEGE OF HAMPTON ROADS
ADDRESS OF CONCERN: 601 Colley Avenue, Norfolk, Virginia 23507
TYPE OF ORGANIZATION:
[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE 26 USC §501(a) and §501(c)(3)
[ ] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE USA
NAME OF STATE: _____ CITATION OF STATUTE: _____
[ ] WOULD QUALIFY AS TAX EXEMPT UNDER 26 USC §501(a) and §501(c)(3) IF LOCATED IN THE USA
[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF USA IF LOCATED IN THE USA
NAME OF STATE: _____ CITATION OF STATUTE: _____

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 13 CFR 1.19(e) for purposes of paying reduced fees under 35 USC §41(a) and (b) with regard to the invention entitled CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS by inventors Gary D. Hodgen described in

[ ] U.S. Patent Application filed herewith
[X] U.S. Patent Application Serial No. 09/059,476 filed April 13, 1998
[ ] U.S. Patent No. _____ issued _____

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having the rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. 37 CFR 1.27.

NAME: _____
ADDRESS: _____
[X] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION
NAME: _____
ADDRESS: _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file in this patent application or patent, notification of any change of status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. 37 CFR 1.29(b).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC §1001, and that such willful false statements may jeopardize the validity of the patent application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: David Thiel
ADDRESS OF PERSON SIGNING: 358 Mowbray Arch, Norfolk, Virginia 23507

SIGNATURE: _____ DATE: April 30 , 1998

Small Entity Status has been established in parent application Serial No. 09/059,476, filed April 13, 1998.

Check No. 084593 which includes the amount of $380.00 in payment of the filing fee is enclosed herewith.

The Patent and Trademark Office is hereby authorized to charge any additional fees or credit any refund, at any time during the prosecution of this application, to Deposit Account No. 15-0700.

Amend the specification at page 1, line 2, after "is", --a divisional of application Serial No. 09/059,476, filed April 13, 1998 which is-- and, on line 3, after "1997", insert --and now abandoned--.

The prior application was assigned to Medical College of Hampton Roads.

The power of attorney in the prior application, as originally filed, is to customer no. 2352, OSTROLENK, FABER, GERB & SOFFEN, LLP, 1180 Avenue of the Americas, New York, New York 10036-8403, and the members of the firm: Reg. No. 17,542; Samuel H. Weiner, Reg. No. 18,510; Jerome M. Berliner, Reg. No. 18,653; Robert C. Faber, Reg. No. 24,322; Edward A. Meilman, Reg. No. 24,735; Stanley H. Lieberstein, Reg. No. 22,400; Steven I. Weisburd, Reg. No. 27,409; Max Moskowitz, Reg. No. 30,576; Stephen A. Soffen, Reg. No. 31,063; James A. Finder, Reg. No. 30,173; William O. Gray, III, Reg. No. 30,944; Louis C. Dujmich, Reg. No. 30,625, and Douglas A. Miro, Reg. No. 31,643, as attorneys with full power of substitution and revocation to prosecute this application, to transact all business in the Patent and Trademark Office in connection therewith and to receive all correspondence. The Power appears in the original papers in the prior application.

P/1890-200(DIV)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patent Application of
Gary D. HODGEN Date: May 18, 1999
Serial No. Unknown
Filed: Herewith
For: CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

Asst. Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to the examination of the foregoing, please amend the application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

Page 4, line 25, change "reception" to --receptor--; and
line 26, change "an" to --a--.

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) In a method of [treating a condition] hormone replacement therapy in a host by administering an effective amount of a selective estrogen receptor modulator to the host to control and regulate estrogenic impact on specific tissues and organs, the

improvement which comprises additionally administering [an effective amount of] an agent which exhibits progestogenic activity to the host in an amount effective to modulate the side effects of the selective estrogen receptor modulator.

Claim 4, line 2, delete "additional"; after "agent" insert --which exhibits progestogenic--.

Claim 10, line 2, delete "additional"; after "agent" insert --which exhibits progestogenic--.

Claim 11, line 2, delete "additional"; after "agent" insert --which exhibits progestogenic--.

Claim 12, line 2, delete "additional"; after "agent" insert --which exhibits progestogenic--.

Claim 13, line 2, delete "additional"; after "agent" insert --which exhibits progestogenic--.

14 (Amended). A kit comprising a plurality of tablets containing an [effective] amount of a selective estrogen receptor modulator effective for hormone replacement therapy and [an effective amount of] an agent which exhibits progestogenic activity in an amount effective to modulate the side effects of the selective estrogen receptor modulator.

Claim 16, line 1, after "agent" insert --which exhibits progestogenic--.

REMARKS

The foregoing amendments have been made to place this case into appropriate condition for consideration and allowance.

For the convenience of the Examiner, submitted herewith is an art listing form setting forth all references cited in the parent cases.

Respectfully submitted,

Edward A. Meilman
Registration No.: 24,735
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700

EXPRESS MAIL CERTIFICATE

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee (mail label #EL010282840US) in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on May 18, 1999:

Dorothy Jenkins
Name of Person Mailing Correspondence

Signature

May 18, 1999
Date of Signature

EAM:mgs

CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

This is a continuation-in-part of application Serial No. 08/888,183, filed July 3, 1997.

BACKGROUND OF THE INVENTION

The use of estrogens in the course of treatment of a variety of conditions is well known. For example, the most prevalent form of oral contraception is the so-called combined oral contraceptive preparation, a pill that combines both estrogen and a progestin. Apparently, the progestin acts foremostly to block gonadotropin release while the estrogen component primarily provides endometrial control to diminish breakthrough bleeding. Another well-known use is long term estrogen replacement therapy which is common for post-menopausal and other estrogen deficient women. Other estrogen dependent conditions include endometriosis, uterine fibroid tumors (leiomyomata), pre-menstrual syndrome, dysfunctional uterine bleeding, breast tumors (benign and malignant) and the like.

Despite their value, estrogen treatments are also associated with undesirable side effects. For example, estrogen therapy has been associated with an increased incidence of endometrial cancer, especially due to the continual "unopposed" estrogen-induced proliferation of the endometrium. Other side effects include uterine bleeding and cyclotherapeutic withdrawal menstrual bleeding during a time in their lives when many women welcome cessation of menstrual bleeding as a normal occurrence in menopause. Estrogen therapy has also been

implicated in the development of a variety of disorders including gallbladder disease, hypertension, abnormal glucose tolerance, hypercoagulable states and breast cancer, although some of these observations are antidotal in nature and have not been confirmed.

There have been numerous efforts to counteract the ill effects of estrogen therapy. For instance, attempts have been made to couple estrogen therapy with short periods of anti-estrogen supplementation. Another approach is to use anti-estrogens in place of the estrogen. Certain compounds are known as "anti-estrogens" because they can bind to the estrogen receptors and competitively block the binding of the more potent estrogens such as estradiol. Among the best known of these anti-estrogens are clomiphene and tamoxifen. However, all such anti-estrogens can be, in fact, active estrogens depending on the tissue, dose/regimen and hormonal milieu of the drug exposure. These are mixed function agonistic/antagonistic activities. The degree to which the anti-estrogen acts as an estrogen also depends on the particular material and the tissue site.

While anti-estrogen therapy has been successful, it is not without its own problems. As is know, there is a hypothalamic-pituitary-gonadal axis involved in endogenous hormone production. As estrogen binds to its receptors, there is a feedback mechanism which regulates the endogenous production of pituitary gonadotropins and, in turn, estrogen so that the hormonal milieu remains within the physiological range. When an anti-estrogen binds to the estrogen receptors, altered estrogen feedback mechanisms are implicated in a pharmacological manner compared to when estrogen binds normally. The anti-estrogens themselves can induce

multiple follicular growth which, in turn, causes the production of endogenous ovarian estrogens. A favorable example is the use of clomiphene for ovulation induction. For the first anti-estrogen dose administration and continuing for some period of time, the endogenous estrogen produced as a consequence of the multiple follicular growth may not appear to pose a problem. However, at some point, which is totally unpredictable and which varies from individual to individual, endogenous estrogen can be produced such that the quantity of estrogen present can elevate blood levels well above 300 pg/ml. Indeed, estradiol concentration in plasma may exceed a few thousand in some instances. Therefore, while the use of an anti-estrogen seeks to reduce or modify or eliminate the side effects of estrogen, its use over time may have the reverse effect by inducing an excess concentration of estrogen. Not only may the use of the anti-estrogen exaggerate the estrogen side effects which it seeks to avoid, but the anti-estrogen may also even eliminate the primary benefit of the administration in the first instance. For example, a "run away" endogenous estrogen can induce ovulation in those situations where the administration of the anti-estrogen was designed to provide contraception. This feature of anti-estrogen therapy makes the establishment and maintenance of appropriate dosages of anti-estrogen difficult and in some cases impossible, especially when the therapeutic goal is simultaneous to limit excessive estrogenic impact in one tissue, while itself providing adequate estrogenic stimulation in another tissue.

It is therefore the object of the present invention to keep the hypothalamus and pituitary from

becoming deranged and thereby prevent multiple follicular growth and the endogenous estrogen sustained, supraphysiological elevations which result from ovarian hyperstimulation. This and other objects of the invention will become apparent to those of ordinary skill in the art from the following detailed description.

SUMMARY OF THE INVENTION

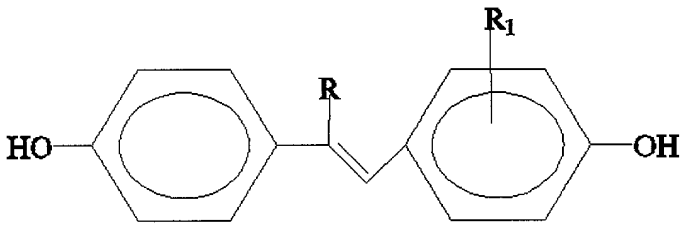
This invention relates to a method of using a SERM such as clomiphene, for instance, pre- and postmenopausally, e.g., in hormone replacement therapy to prevent osteoporosis, cardiovascular disease and breast cancer, as well as preventing the hypothalamus and pituitary from operating in a deranged manner during any SERM therapy. More particularly, the invention involves superposing upon the use of a selective estrogen receptor modulator, the co-administration of a compound progestationally active to women, either of reproductive age women who are pre-menopausal or who are post-menopausal. The progestationally active compound may also exhibit androgenic activity or an androgenically active compound can be coadmistered.

DETAILED DESCRIPTION OF THE INVENTION

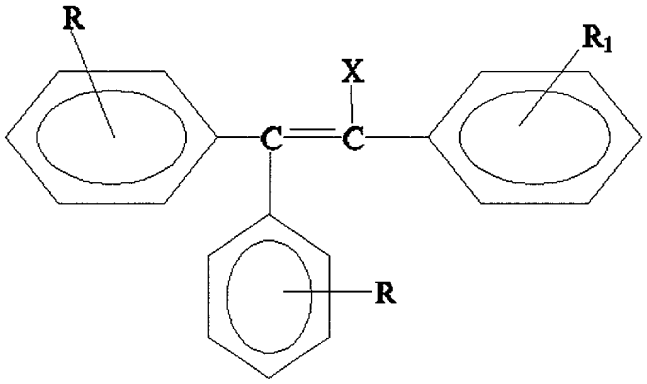
In accordance with the present invention, an additional hormonal therapy is superposed upon the use of a selective estrogen reception modulator (also known as an SERM, selective estrogen or anti-estrogen) in the known use of the SERM, for instance, as in treating or controlling an estrogen sensitive condition. Estrogen sensitive conditions include, but are not limited to, contraception, hormone replacement therapy, endometriosis, leiomyoma, dysfunctional uterine bleeding,

premenstrual syndrome, hormonal dependent cancers, such as those of the breast, endometrial and ovarian, and the like. Some SERMs have been indicated for the prevention of post-menopausal osteoporosis, modulation of serum lipid profiles and breast cancer prevention.

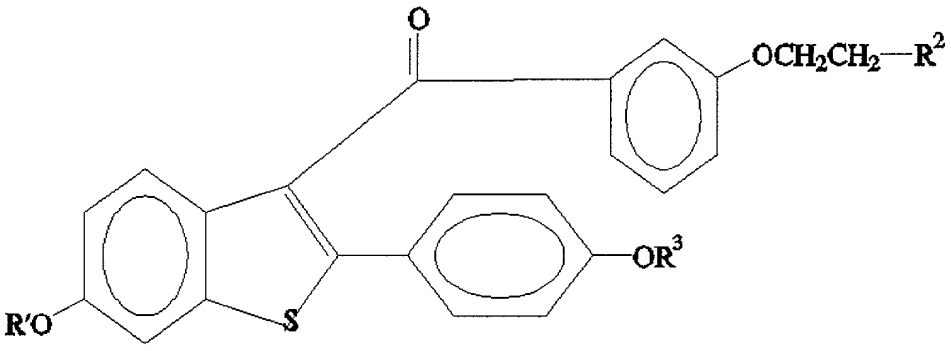
Any known SERM can be used in the practice of this invention for its known utility in the treatment or modification of a medial condition in mammals. Examples of known SERMs include, but are not limited to, clomiphene; cycladiene; tamoxifen; nafoxidine; nitromifene citrate (N-55,945-27); 13-ethyl-17α-ethynl-17β-hydroxygona-4-9-11-trien-3-one (R2323); diphenol hydrochrysene; erythro-MEA; allenolic acid; cyclofenyl; chlorotrianisene; ethamoxytriphetol; triparanol; CI-626; CI-680; MER-25; U-11,555A; U-11,100A; ICI-46,669; ICI-46,474; CN-55,945; compounds of the formula:



where R_1 is hydrogen, an aromatic group or alkyl of preferably no more than nine carbon atoms, R is an aromatic or alkyl group of preferably no more than nine carbon atoms and various of their derivatives; the triphenyl compounds described in U.S. Patent 2,914,563 which are of the formula:



wherein one of the R groups is a basic ether of the formula $OC_nH_{2n}A$ in which n is 2, 3 or 4 and A is a C_{1-4} dialkylamino group, N-piperidyl or β-morpholinyl and the other R and R_1 are hydrogen, halogen or methoxy while X is halogen; as well as benzothiophenes such as those described in U.S. Patent 5,624,940 of the formula:



in which R^1 and R^3 are independently hydrogen, C_{1-4} alkyl, $-CO(C_{1-6}alkyl)$ or -COAr in which Ar is optionally substituted phenyl, R^2 is pyrrolidino, hexamethyleneamino or piperidino, or a salt thereof. Example of the benzothiophenes include raloxifene (6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinethoxy)-

benzoyl]benzo[b]thiophene) and LY353381.HCl benzothyphenes. The SERMs can also be employed in the form of their pharmaceutical acceptable non-toxic salt or complexes. Examples include the acid addition salt such as, for instance, citrate, hydrochloride, hydrobromide, sulfate, phosphate, nitrate, oxalate, fumarate, gluconate, tannate, maleate, acetate, benzoate, succinate, alginate, malate, ascorbate, tartrate and the like. The complexes can be with metals or various organic moieties.

The SERM aspect of the present invention is similar to the previous use of such materials for the treatment of estrogen dependent or other medical conditions. Thus, not only may any known SERM be employed, but also the dosage amount and mode of administration heretofore employed can also be employed in the practice of the present invention. Those SERMs which have an asymmetric atom can be used as the racemate or in any of the chiral or entomeric forms or mixture of such forms. For example, clomiphene can be used with an array of isomeric ratios (EN:ZU), as well as employing only one of the isomers. Thus, the route of administration can be in any conventional route where the SERM is active, for instance orally, intravenously, subcutaneously, intramuscularly, sublingually, percutaneously, rectally, intranasally or intravaginally. Similarly, the administration form can be a tablet, dragee, capsule, pill, nasal mist, aerosol, pellet, implant (or other depot) and the like.

Superposed on the SERM administration is the use of a progestationally active compound, optionally with androgenic activity or in combination with an androgenically active compound. The additional agent can

be progesterone, a synthetic progestin analog or even an anti-progestin having agonistic activity (i.e., progestin-like activity without relying on its "non-competitive anti-estrogenic" properties). Examples of progestins which can be utilized include progesterone, medroxyprogesterone acetate, norgesterel, levo-norgesterol, norethindrone and its esters, norethynodrel, ethynodiol diacetate, chlormadione acetate, cyproterone and its esters, norethindrone, gestodene, desogestrel, norgestimate, and the like. Examples of androgenic compounds include low doses of testosterone, androsteridione and DHT. Some compounds such as danazol and levonorgestrel exhibit both androgenic and progestogenic activity simultaneously.

The antiprogestin can be a progesterone receptor antagonist or any pharmaceutically suitable agent that counteracts the normal biological activity of progesterone. A preferred antiprogestin is a progesterone receptor antagonist. For example, RU 486 is particularly suitable in the practice of this invention.

Examples of antiprogestins which can be employed in this invention are RU 486 ("mifepristone", Roussel Uclaf, Paris; U.S. patent 4,386,085); and the steroids described in the following patents and patent applications: U.S. Patent 4,609,651, especially the compound lilopristone (11ß-(4-dimethylaminophenyl)-17ß-hydroxy-17α-(3-hydroxy-prop-1-(Z)-enzyl-4,9(10) estradien-3-one); U.S. application Serial No. 06/827,050, especially the compounds 11ß-(4-acetylphenyl)-17ß-hydroxy-17α-(1-propenyl)-4,9-estradien-3-one and 11ß-(4-acetylphenyl)-17ß-hydroxy-17α-(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one; U.S. application Serial No.

07/283,632; U.S. Patent 5,095,129; and other anti-gestations, e.g., U.S. Patent 4,891,368.

Other examples of progestinally active compounds are well known in the art.

The amount of progestationally and optional androgenically active compound which is administered is that which is effective to regulate endogenous estrogen secretions to a desired level. Thereby, ovulation can be blocked and endometrial growth and menstruation can be controlled. As a general proposition, the blood estrogen (endogenous) concentration achieved can be in the range of about 25 to 125 pg/ml and more preferable about 60 to 90 pg/ml, although other values can be selected if desired.

The progestinally and optional androgenically active compound can be administered by way of any art recognized means as practiced in the pharmaceutical arts. For example, it can be formulated in combination with the SERM or separately so that it is administered orally, subcutaneously, intramuscularly, buccally, by a skin patch for transdermal absorption, contained within an inert matrix which is implanted within the body and in the depot state or intravaginally in a matrix that releases the material.

Formulations containing the SERM or the progestationally active and optional androgenically active compound, together with a suitable carrier, can be a solid dosage form which includes tablets, capsules, cachets, pellets, pills, powders and granules; topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies and foams; and parential dosages forms which include solutions, suspensions,

emulsions or dry powder. The composition can in addition contain a pharmaceutical acceptable diluents, fillers, disintegrates, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humeticants, moisturizers, solubilizers, preservatives and other means of augmenting the medicinal entity. The means and methods of administration are known in the art and the artisan can refer to various pharmalogic references for guidance. One such reference is "Modern Pharmaceuticals", Banker & Rhodes, Marcel Dekker, Inc. 1979 and another is Goodman & Gilman's, "The Pharmaceutical basis of therapeutics", 6th Ed., MacMillan Publishing Co., New York, 1980.

If desired, the two (or three) components, namely the SERM and the progestationally active and optional androgenically active compound, can be coadministered utilizing the same or different dosage forms or means, for example for the same tablet. Application of the components, compositions and the methods of this invention for the medical and/or pharmaceutical use which are described in this text can thus be accomplished by any clinical, medical or pharmaceutical methods or techniques as are presently or prospectively known to those skilled in the art.

The administration of the components can be either periodic such as a weekly basis or continuous, that is on a daily administration. Daily administration is preferred because individuals are more likely to follow the treatment regimen and not to forget or overlook a periodic administration schedule. Amounts can be lowered or raised based on the administration regimen and based on the characteristics of the individual receiving the treatment. Variations of dosage based or

the route of administration may vary and such changes can be determined practicing known techniques.

The pharmaceutical formulations can be provided in kit form containing a plurality of dosage units intended for ingestion on successive days. Preferably, the plurality is in multiples of seven.

In order to further illustrate the present invention, specific examples are set forth below. It would be appreciated, however, that these examples are illustrative only and are not intended to limit the scope of the invention.

Examples

1. Clomiphene is used alone at 100 mg/day for the treatment of endometriosis. After 15 days, the serum estrogen reached 500 pg/ml. Levonorgestrel at 75 mcg/day is then also administered. The serum estrogen retreated to physiological value.

2. Raloxifene at 500 mg/day and medroxprogesterone acetate at 12 mg/day were administrated to treat leiomyoma. Serum estrogen remained at physiological levels.

3. Example 1 is repeated using clomiphene EN:ZU isomers in a ratio of 8:1.

4. Clomiphene ZU isomer at 50 mg/day and norgestimate at 100 mcg/day are coadministered while the serum estrogen remained at physiological levels.

5. Clomiphene is used alone at 100 mg/day for the treatment of endometriosis. After 15 days, the serum estrogen reached 500 pg/ml. Danazol at 100 to 800 mg/day is then also administered. The serum estrogen retreated to physiological value.

6. Example 5 is repeated using testosterone at a dosage of 2 to 10 mg/day in place of the danazol.

WHAT IS CLAIMED IS:

1. In a method of treating a condition in a host by administering an effective amount of a selective estrogen receptor modulator to the host to control and regulate estrogenic impact on specific tissues and organs, the improvement which comprises additionally administering an effective amount of an agent which exhibits progestogenic activity to the host.

2. The method of claim 1 wherein the selective estrogen receptor modulator is clomiphene.

3. The method of claim 1 wherein the selective estrogen receptor modulator is a benzothiophene.

4. The method of claim 1 wherein the additional agent is an antiprogestin.

5. The method of claim 4 wherein the antiprogestin is a progesterone receptor antagonist.

6. The method of claim 5 wherein the selective estrogen receptor modulator is clomiphene.

7. The method of claim 5 wherein the selective estrogen receptor modulator is a benzothiophene.

8. The method of claim 4 wherein the amount of antiprogestin is that sufficient to maintain the blood

estrogen concentration in the range of about 25 to 125 pg/ml.

9. The method of claim 8 wherein the amount of antiprogestin is that sufficient to maintain the blood estrogen concentration in the range of about 60 to 90 pg/ml.

10. The method of claim 1 wherein the additional agent expresses both androgenic and progestogenic activity.

11. The method of claim 10 wherein the additional agent comprises the combination of an androgen and a progestin.

12. The method of claim 10 wherein the additional agent is a single material which expresses both activities.

13. The method of claim 12 wherein the additional agent is danazol or levonorgestrel.

14. A kit comprising a plurality of tablets containing an effective amount of a selective estrogen receptor modulator and an effective amount of an agent which exhibits progestogenic activity.

15. The kit of claim 14 wherein the selective estrogen receptor modulator is clomiphene or a benzothiophene.

16. The kit of claim 14 wherein the agent is an antiprogestin.

17. The kit of claim 16 wherein the antiprogestin is a progesterone receptor antagonist.

18. The kit of claim 14 wherein the agent expresses both androgenic and progestogenic activity.

19. The kit of claim 18 wherein the agent comprises the combination of an androgen and a progestin.

20. The kit of claim 18 wherein the agent is a single material which expresses both activities.

P/1890-162

CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

ABSTRACT OF THE DISCLOSURE

The treatment of an estrogen sensitive condition by the administration of a selective estrogen receptor modulator is improved by additionally administering a progestationally active compound to the recipient. The additional agent can express both progestational and androgenic activity or an androgenically active material can be employed, if desired. Additionally, clomiphene in an array of isomeric ratios (EN:ZU) can be used alone for prevention of osteoporosis, maintenance of a healthful blood lipid profile, and prevention of breast tumors, or to sustain amenorrhea.

UNITED STATES OF AMERICA COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	OFGS FILE NO. P/1890-162

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CONTROL OF SELECTIVE ESTROGEN RECEPTOR MODULATORS

the specification of which is attached hereto, unless the following box is checked:

☒ was filed on April 13, 1998 as United States patent Application Number or PCT International patent application number 09/059,476 and was amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information known to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate or United States provisional application(s) listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign or Provisional Application(s)

COUNTRY	APPLICATION NUMBER	DATE OF FILING *(day, month, year)*	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			YES ____ NO ____
			YES ____ NO ____
			YES ____ NO ____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

UNITED STATES APPLICATION NUMBER	DATE OF FILING *(day, month, year)*	STATUS *(patented, pending, abandoned)*

I hereby appoint customer no. 2352 OSTROLENK, FABER, GERB & SOFFEN, LLP, and the members of the firm, Marvin C. Soffen - Reg. No. 17,542; Samuel H. Weiner - Reg. No. 18,510; Jerome M. Berliner - Reg. No. 18,653; Robert C. Faber - Reg. No. 24,322; Edward A. Meilman - Reg. No. 24,735; Stanley H. Lieberstein - Reg. No. 22,400; Steven I. Weisburd - Reg. No. 27,409; Max Moskowitz - Reg. No. 30,576; Stephen A. Soffen - Reg. No. 31,063; James A. Finder - Reg. No. 30,173; William O. Gray, III - Reg. No. 30,944 and Louis C. Dujmich - Reg. No. 30,625, as attorneys with full power of substitution and revocation to prosecute this application, to transact all business in the Patent & Trademark Office connected therewith and to receive all correspondence.

SEND CORRESPONDENCE TO: OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036-8403
CUSTOMER NO. 2352

DIRECT TELEPHONE CALLS TO:
(212) 382-0700

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Gary D. Hodgen	Gary D. Hodgen	4-27-98

RESIDENCE *(City and either State or Foreign Country)*	COUNTRY OF CITIZENSHIP
3844 Church Point Road, Virginia Beach, Virginia 23455	U.S.A.

POST OFFICE ADDRESS
Same as above

FULL NAME OF SECOND JOINT INVENTOR (IF ANY)	INVENTOR'S SIGNATURE	DATE

RESIDENCE *(City and either State or Foreign Country)*	COUNTRY OF CITIZENSHIP

POST OFFICE ADDRESS

FULL NAME OF THIRD JOINT INVENTOR (IF ANY)	INVENTOR'S SIGNATURE	DATE

RESIDENCE *(City and either State or Foreign Country)*	COUNTRY OF CITIZENSHIP

POST OFFICE ADDRESS